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ORIGINAL ARTICLE

The contribution of immobility risk factors to the incidence of venous thrombosis in an older population

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Summary. *Background:* Venous thrombosis is common in the older population. Assessment of risk factors is necessary to implement preventive measures. *Objectives:* We studied the associations between immobility-related risk factors and thrombosis, specifically, hospitalization, surgery, fractures, plaster cast use, minor injuries, and transient immobility at home, in an older population. *Patients and Methods:* Analyses were performed in the Age and Thrombosis, Acquired and Genetic risk factors in the Elderly (AT-AGE) study, a two-center population-based case-control study. Consecutive cases aged > 70 years with a first-time thrombosis (n = 401) and control subjects > 70 years old without a history of thrombosis (n = 431) were included. Exclusion criteria were active malignancy and severe cognitive disorders. We calculated odds ratios (OR) with 95% confidence intervals (95% CI) after adjustment for age, sex, body mass index, study center, and population-attributable risks. *Results:* There was a 15-fold (OR 14.8, 95% CI 4.4–50.4) increased risk of thrombosis within 2 weeks after hospital discharge. Surgery (OR 6.6, 95% CI 3.7–11.6), fractures (OR 12.7, 95% CI 3.7–43.7), plaster cast (OR 6.2, 95% CI 2.0–18.9), minor leg injuries (OR 1.9, 95% CI 1.1–3.3), and transient immobility at home (OR 5.0, 95% CI 2.3–11.2) were all associated with thrombosis risk over 3 months. The population-attributable risks for in-hospital immobility was 27%, and for out-of-hospital immobility, 15%. *Conclusions:* In those > 70 years of age, in-hospital and out-of hospital immobility are strong risk factors for thrombosis. Additional studies on preventive measures during immobilization in this age group should not focus solely on hospital settings.

Keywords: aged; immobilization; population at risk; pulmonary embolism; risk factors; venous thrombosis.

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Introduction

Venous thrombosis presents mainly as deep venous thrombosis of the leg (DVT) and pulmonary embolism (PE). The incidence of thrombosis increases sharply with age, being rare in young individuals (< 1 per 10 000 per year) and increasing to approximately 1% per year in very old age [1]. More than two-thirds of all patients with venous thrombosis are aged ≥ 60 years, and 25% are older than 80 years [2]. So, increasing age is one of the most important risk factors. As venous thrombosis is a potentially lethal disease, morbidity (e.g. the postthrombotic syndrome) is common, and treatment has frequent side effects, prevention efforts will have large effects in older individuals [3]. However, the risk factors for thrombosis in the older population are not well characterized since studies to date mainly included young and middle-aged individuals [4].

Immobility is associated with reduced venous blood flow, particularly in the pockets of the venous valves, leading to inflammation and hypercoagulability [5,6]. In young and middle-aged individuals, immobility, such as that due to hospitalization or minor injuries, is an established risk factor for thrombosis with relative risk estimates ranging from 3 to 11 [7,8]. However, it is unknown to what extent immobilization increases the risk of venous thrombosis in older individuals. We hypothesized that immobility-related risk factors would be strong risk factors in this population.

The aim of this study was to assess the risk of venous thrombosis associated with hospitalization, surgery, use of a plaster cast, minor injury, and transient immobility at home in a case–control study of people aged ≥ 70 years.

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Methods

Identification of participants

The Age and Thrombosis, Acquired and Genetic risk factors in the Elderly (AT-AGE) Study is a two-center, population-based case–control study in Leiden, the Netherlands, and Burlington, VT, USA, designed to study risk factors for venous thrombosis in the older population. From June 2008 to August 2011 in Leiden and December 2008 to July 2011 in Burlington, all consecutive patients aged ≥70 years with DVT or PE were identified.

In Leiden, cases were identified from two anticoagulation clinics in a defined geographical area in the western part of the Netherlands. In Burlington, cases were identified in the Vascular Laboratory and the Radiology Department of Fletcher Allen Health Care, Burlington, VT, which are the only diagnostic centers in that geographic area. We defined venous thrombosis as DVT alone or PE with or without a proven DVT by ultrasound (PE with or without DVT). We were unable to accurately define isolated PE without DVT since diagnostic measures of thrombosis of the legs are not routinely performed in all PE patients. Control subjects were identified in Leiden and Burlington in the same geographic area as the cases. Control subjects were randomly selected from five primary care practices in Leiden and four in Burlington.

All identified cases and control subjects were mailed an invitation letter, followed by a telephone call to discuss participation. Individuals were excluded from participation if they responded affirmatively that they had an active malignancy, defined as diagnosis of cancer within 6 months before the thrombotic event (or date of telephone call for the control subjects) or chemotherapy or radiation therapy for cancer in the past 6 months. Potential participants with severe psychiatric or cognitive disorder, as judged by the telephone contact, were excluded. We also excluded individuals who self-reported previous DVT or PE within the past 10 years.

Of the 1187 identified cases, 689 (58%) were eligible and 498 (42%) were excluded. (Fig. 1) Of those excluded, 55 (11%) died before inclusion was possible, 159 (32%) had active malignancy, 108 (22%) had an apparent severe cognitive or psychiatric disorder, and 171 (34%) had a history of venous thrombosis within the past 10 years. Of the 723 identified control subjects, 631 (87%) were eligible and 92 (13%) were excluded: 15 (16%) died before inclusion was possible, 19 (21%) had active malignancy, 34 (37%) had an apparent severe cognitive or psychiatric disorder, and 10 (11%) had a history of venous thrombosis within the past 10 years (see Fig. S1 for participation flowchart by study center).

All participants provided written informed consent in accordance with the Declaration of Helsinki and gave permission to obtain information about their medical history. The study was approved by the Medical Ethical Committee of the Leiden University Medical Center and by the Committee of Human Research of the University of Vermont.

Data collection

In Leiden, 398 (71%) of the 561 invited cases and 321 (76%) of the 422 invited control subjects participated. In Burlington, 128 cases were invited and 75 (59%) participated, while 140 (67%) of the 209 invited control subjects participated. For all eligible cases and controls subjects who agreed to participate, home visits were scheduled. During this home visit, an extensive structured interview and blood collection were completed by trained personnel. The index date was defined as the date of diagnosis of the thrombosis for the cases and the date of the in-home interview for the control subjects.

The interview assessed thrombosis risk factors that have been established in the young and middle-aged as well as other putative age-specific risk factors that were present within 3 months of the index date. Questions queried hospitalizations, surgery during hospitalization, fractures and use of plaster cast (or splint), minor injuries of the lower extremities, and transient immobility at home, including dates and location. Physical measurements were performed including weight (measured with a calibrated scale) and height. Body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m^2).

Analyses

For these analyses on the etiology of thrombosis, we included only cases and control subjects without a history of venous thrombosis (403 cases and 433 control subjects) who had complete interview data (401 cases and 431 control subjects). Characteristics of the control subjects included in Leiden and in Burlington were analyzed separately to provide insight into the source populations. For all further analyses, we combined data from the two sites. We determined associations between transient immobility–related risk factors and venous thrombosis. Transient immobility was defined as a status of immobility that is shortly present in one's life. As estimates of relative risk, we calculated odds ratios (OR) and their 95% confidence intervals (95% CI) using logistic regression models. All reported ORs were adjusted for age (continuous), sex, BMI (continuous), and study center using multivariable logistic regression analysis. Stratified analyses were performed for DVT and for PE with or without DVT.

Hospitalization was defined as present when the participant was hospitalized at the index date or the discharge date was within the 3-month window previous to the index date. Hospital admission for both inpatients and day patients were taken into account. Hospitalization for surgical and nonsurgical indications was analyzed separately. The presence of a fracture or plaster cast (or

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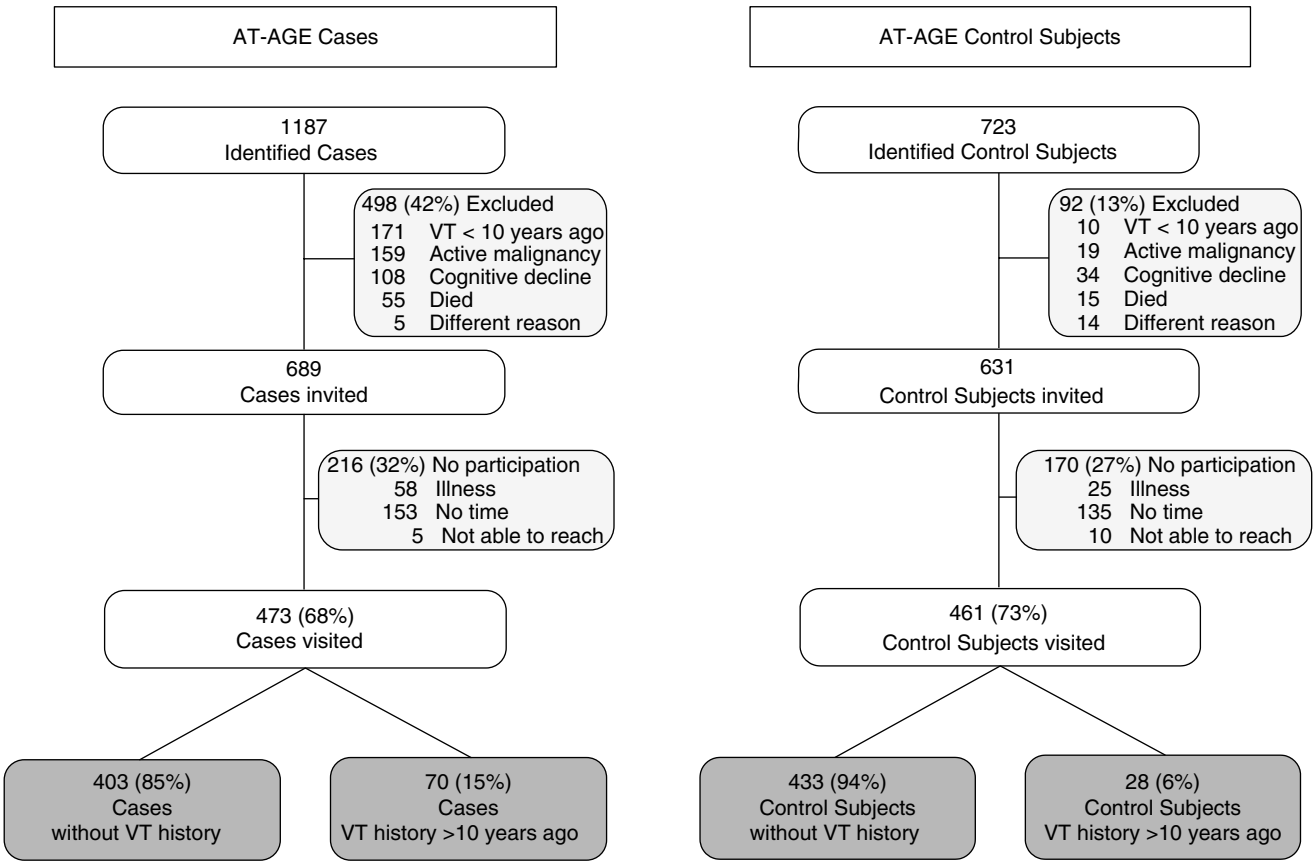

Fig. 1. Flowchart of AT-AGE study.

splint) in the 3 months before the index date were analyzed as putative risk factors, as were minor injuries of the lower extremities and transient immobility at home. A minor injury was defined as an injury of the lower extremities (hip, knee, ankle, or foot) such as a sprained ankle or contusion of the lower leg that started within the 3-month window. A period of transient immobility at home was defined as a period of ≥ 4 consecutive days of immobility, such as being bedridden or continuously sitting in a chair, that started within the 3 months before the index date. If participants were bed- or chair-ridden for the entire 3 months before the index date, they were classified as chronically immobilized and not included in the analyses.

To study the duration of risk of venous thrombosis after the transient risk factor, we dichotomized the time between the risk factor and venous thrombosis by the median time from the end of the risk period (for hospitalization) or the start of the risk period (for minor injury or transient immobility at home) in the control subjects. Since the group of participants with hospitalization in the 3 months before the index date was large enough for further stratification, to study the time trend in risk of venous thrombosis in more detail, the time after hospital discharge was divided into three periods (< 2 weeks, 2–4 weeks, and 4 weeks–3 months). The small number of control subjects with fractures or plaster cast prohibited a detailed analysis of the risk by time from immobilization.

In addition, a sensitivity analysis was performed. Since the index date was defined as the date of the home visit for the control subjects and therefore, per definition, none of the controls were hospitalized on the index date, assessment of the risk of thrombosis during hospitalization was not directly possible. To estimate the risk of venous thrombosis during hospitalization, the index date of the controls was moved back by 5 weeks (i.e. by the median time [in weeks] of the cases between diagnosis of thrombosis and home visit).

We calculated population attributable risk (PAR) as: $pd(OR - 1)/(OR)$, in which pd is the proportion of cases exposed to the risk factor of interest. In this case, the PAR indicates the proportion of the total incidence of venous thrombosis in those ≥ 70 years old who were eligible for this study that can be attributed to the risk factor of interest [9,10]. We calculated the PAR for all immobility-related risk factors combined and for in-hospital and out-of-hospital immobility, separately. Out-of-hospital immobility was defined as the presence of fractures, plaster cast (or splint), minor injuries, and transient immobility at home within the nonhospitalized population.

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Results

For the cases, the median duration between the index date and the home visit was 5 weeks (range 1–44 weeks), 75% were visited within 7 weeks, and 90% were visited within 10 weeks. General characteristics of the control subjects in Leiden and Burlington are shown in Table 1. In both centers, ~30% of the control subjects were ≥ 80 years old. Median BMI was slightly higher in Burlington than in Leiden. Of the 401 cases, in Leiden, 134 (39%) of the cases had DVT, and 207 (61%) had PE with or without DVT, and in Burlington, 32 (53%) had DVT and 28 (47%) had PE with or without DVT. In 155 of the 166 DVT cases (93%) and in 220 of the 235 PE cases (94%), we were able to obtain the diagnostic report of the thrombotic event and thrombosis was thus objectively confirmed via ultrasound and PE was confirmed via spiral computed tomography or ventilation-perfusion lung scan.

Table 2 shows the risk of venous thrombosis associated with immobility-related risk factors. Overall, hospitalization was associated with a greater than 7-fold increased risk of venous thrombosis (OR 7.2, 95% CI 4.5–11.4). Among cases and controls with hospitalization, the median duration of hospital stay in the cases was 10 days (range 2–55 days), and in the control subjects, 3 days (range 1–22 days). Dichotomization of the time between discharge from hospital and the index date, based on the median time of hospitalization until the index date in the control subject (48 days, range 4–89), showed that the risk of venous thrombosis was 7.9-fold increased in the first 7 weeks after discharge (OR 7.9, 95% CI 4.2–14.7) and 2.1-fold increased after 7 weeks (7 weeks–3 months, OR 2.1, 95% CI 1.0–4.4). Further stratification of the time between hospital discharge and the index date showed a 14.8-fold increased risk of thrombosis within the first 2 weeks after discharge from the hospital (OR 14.8, 95% CI 4.4–50.4) and gradually decreasing risk to a 3-fold increased risk between 2 weeks and 3 months after discharge (Table 3). Performing a sensitivity analysis using the recalculated index date for the controls, 41 (10.1%) cases and 1 (0.2%) control subject were hospitalized during the index date, indicating that the thrombotic risk was highest during hospitalization, although the CI was wide (OR 48.7, 95% CI 6.6–361.0).

Among the cases hospitalized within the 3 months before the index date, 79 of the 126 (63%) had surgery during the hospital admission. When compared with individuals without hospitalization, the risk of venous thrombosis associated with surgery-related hospitalizations (OR 6.6, 95% CI 3.7–11.6) was similar to that for non–surgery-related hospitalizations (OR 5.5 95% CI 2.7–10.4, OR for surgical versus nonsurgical admission 1.1, 95% CI 0.4–2.7). Thirty-one (7.8%) of the cases and 4 (0.9%) of the control subjects underwent lower extremity surgery, indicating that lower extremity surgery was associated with an almost 9-fold increased risk of thrombosis (OR 8.6, 95% CI 3.0–25.1).

Fracture was associated with a nearly 13-fold increased risk of thrombosis (OR 12.7, 95% CI 3.7–43.7). In the cases, two-thirds of fractures ($n = 17$) were of the lower extremities; of these patients, eight (47%) presented with a DVT. In 87% of these cases, the DVT was diagnosed on the ipsilateral side as the fracture. Use of a plaster cast or a splint was associated with a 6-fold increased risk of thrombosis (OR 6.2, 95% CI 2.0–18.9).

Minor leg injury was associated with a 1.9-fold increased risk of thrombosis (OR 1.9, 95% CI 1.1–3.3). The median time of occurrence of the minor injury until the index date was 43 days (range 1–92) for the cases and 27 days (range 4–93) for the controls. Compared with individuals without a minor injury in the 3 months before the index date, the risk of venous thrombosis was 1.3-fold (95% CI 0.6–2.7) increased in the first 4 weeks after start of the minor injury and remained 2.8-fold (95% CI 1.3–5.8) increased between 4 weeks and 3 months after the start of the immobility. The risk of thrombosis was increased in individuals with sprains of the ankle or knee (OR 1.9, 95% CI 0.6–6.1) and a contusion of the leg (OR 1.5, 95% CI 0.7–3.1). In 24 of the 41 cases (59%) with a minor injury, a DVT was diagnosed, while 17 cases (41%) had PE with or without DVT. In 22 of these 24 cases (92%), the DVT was diagnosed on the ipsilateral side as the minor injury.

Transient immobilization was associated with a 5-fold increased risk of thrombosis (OR 5.0, 95% CI 2.3–11.2).

Table 1 Characteristics of control subjects by center

	Control subjects, Leiden	Control subjects, Burlington
No. of participants	306	125
Median age, *n* (range)	76 (70–94)	76 (70–96)
70–75 years, *n* (%)	126 (41)	49 (39)
75–80 years, *n* (%)	90 (29)	39 (31)
80–85 years, *n* (%)	61 (20)	24 (19)
> 85 years, *n* (%)	29 (10)	13 (11)
Men, *n* (%)	147 (48)	62 (50)
Ethnicity white, *n* (%)*	284 (93)	124 (99)
Smoking status*		
Never, *n* (%)	88 (29)	32 (26)
Former, *n* (%)	168 (55)	87 (69)
Current, *n* (%)	49 (16)	6 (5)
Median BMI (kg m^{-2}) (range)*	25.9 (17.0–42.0)	27.3 (19.0–49.7)
Hospitalization, *n* (%)†	16 (5)	13 (10)
Surgery, *n* (%)†	12 (4)	4 (3)
Fracture, *n* (%)†	1 (0.3)	2 (2)
Plaster cast (splint), *n* (%)†	2 (1)	2 (2)
Minor injury, *n* (%)*†	18 (6)	8 (7)
Transient immobility at home, *n* (%)*†	5 (2)	3 (2)

BMI, body mass index. *Ethnicity 5 missing values, smoking 1 missing value, BMI 8 missing values, minor injury 1 missing value, transient immobility at home 1 missing value. †Less than 3 months before index date.

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Table 2 Association of transient immobility–related risk factors with venous thrombosis

	Cases, $n = 401$	Control subjects, $n = 431$	OR crude (95% CI)	Adjusted OR,* (95% CI)
Hospitalization, *n* (%)†	126 (31.4)	29 (6.7)	6.4 (4.1–9.8)	7.2 (4.5–11.4)
Surgery, *n* (%)†	79 (19.7)	16 (3.7)	6.4 (3.6–11.1)	6.6 (3.7–11.6)
Thrombosis after discharge, *n* (%)	84 (67)			
Time after discharge‡				
< 2 weeks (%)	28 (9.3)	3 (0.7)	13.6 (4.1–45.3)	14.8 (4.4–50.4)
2–4 weeks (%)	17 (5.9)	3 (0.7)	8.3 (2.4–28.5)	8.8 (2.5–31.5)
> 4 weeks–3 months (%)	38 (12.1)	22 (5.2)	2.5 (1.5–4.4)	2.9 (1.6–5.1)
Fracture, *n* (%)†	27 (6.7)	3 (0.7)	10.3 (3.1–34.2)	12.7 (3.7–43.7)
Plaster cast (splint), *n* (%)†	21 (5.2)	4 (0.9)	5.9 (2.0–17.3)	6.2 (2.0–18.9)
Minor injury, *n* (%)†‡	41 (10.5)	26 (6.1)	1.8 (1.1–3.0)	1.9 (1.1–3.3)
Start of minor injury (approximately)				
< 4 weeks (%)	15 (4.1)	15 (3.6)	1.1 (0.6–2.4)	1.3 (0.6–2.7)
> 4 weeks–3 months (%)	26 (6.9)	11 (2.7)	2.7 (1.3–5.6)	2.8 (1.3–5.8)
Transient immobility at home, *n* (%)†‡	34 (8.8)	8 (1.9)	5.1 (2.3–11.1)	5.0 (2.3–11.2)
Start of transient immobility‡				
< 9 weeks (%)	25 (6.6)	4 (0.9)	7.5 (2.6–21.7)	7.7 (2.6–22.9)
> 9 weeks–3 months (%)	9 (2.5)	4 (0.9)	2.7 (0.8–8.8)	2.5 (0.8–8.5)

OR, odds ratio, CI, confidence interval. *Adjusted for age (continuous), sex, body mass index (continuous), and study center. †Less than 3 months before index date. ‡Time after discharge: cases: 1 missing value, control subject 1 missing value; minor injury 6 missing values, transient immobility at home: 6 missing values.

Table 3 ORs of thrombosis over 3 months with transient immobility risk factors stratified by type of thrombosis

Exposure	*N*, DVT/total VT (%)	DVT, OR (95% CI)*	PE with or without DVT, OR (95% CI)*
Hospitalization	43/126 (34)	5.6 (3.2–9.8)	9.1 (5.5–15.2)
Surgery	27/79 (34)	5.3 (2.7–10.4)	7.9 (4.2–14.6)
Fracture	11/27 (41)	14.2 (3.7–55.3)	10.9 (2.9–40.5)
Plaster cast (splint)	6/21 (29)	4.2 (1.1–16.5)	7.6 (2.3–24.9)
Minor injury	24/41 (59)	2.6 (1.4–4.9)	1.4 (0.7–2.6)
Transient immobility at home	7/34 (21)	2.4 (0.8–6.8)	7.4 (3.2–17.2)

OR, odds ratio; DVT, deep venous thrombosis of the leg; VT, venous thrombosis; PE, pulmonary embolism; CI, confidence interval. *Adjusted for age (continuous), sex, body mass index (continuous), and study center.

Median duration of transient immobilization at home was 8 days (range 4–77 days) in the cases and 10 days (range 4–30 days) in control subjects. The median time of the start of transient immobility until the index date was 27 days (range 2–81) for the cases and 63 days (range 38–86) for the control subjects. The risk of thrombosis was 7.7-fold increased (95% CI 2.6–22.9) within the first 9 weeks (63 days) after the transient immobility, whereas as an OR of 2.5 (95% CI 0.8–8.5) was found if transient immobility was > 9 weeks up to 3 months earlier. In 42% of the cases, the reason for transient immobilization at home was an infection, 23% had generalized weakness or 'malaise,' 17% had fracture, and 9% each had back pain or a minor injury. Of the cases, 5 (1.2%) were chronically immobilized, whereas none of the control subjects were chronically immobilized.

All immobility risk factors were similarly associated with both DVT and PE with or without DVT. (Table 3) Overall, immobilization from any cause had a PAR of 39%. In-hospital immobility and out-of-hospital immobility had PARs of 27% and 15%, respectively.

Discussion

In the AT-AGE study, a case–control study on venous thrombosis risk in people aged ≥ 70 years, we determined that immobility-related risk factors (i.e. hospitalization, surgery, fractures, plaster cast [or splint], minor injuries of the legs, and transient immobility at home) were strongly associated with the risk of venous thrombosis (both DVT and PE with or without DVT) in the 3 months after the start of the immobility (OR 2–13). The highest risk of thrombosis was for found for immobilization during hospitalization (OR 48.7, 95% CI 6.6–361.0), and the risk of thrombosis out-of hospital was 15-fold increased within the 2 weeks after hospital discharge; the risk remained increased for 3 months after hospital discharge. Predefined potential confounders of the risk factors (i.e. age, sex, BMI, and study center) did not alter any of the associations. Previous studies on immobility and the risk of thrombosis in older populations reported similar risk estimates, ranging from 1.5- up to > 8-fold increased risks. [4] Based on the PARs we

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observed, the overall contribution of immobility to thrombotic risk (both in and out of hospital) in this study population was 40%. A PAR of 27% was found for in-hospital–related immobility. This contrasts with data previously reported for younger people, where the PAR was only 15% for hospital-related immobility [4]. Importantly, the PAR was 15% for out-of-hospital immobility in the past 3 months in this older population. These findings indicate that immobility explains part of the age gradient in the incidence of venous thrombosis.

Findings illustrate the large impact of immobility, a common occurrence in the older population. The prevalence of immobility-related risk factors in the 3 months before the index date for our control group ranged from 2% to 8% for the different exposures.

Hospitalization causes immobilization [11]. In line with this, we found that cases were hospitalized for a longer period than the control subjects. One should take into account that severity and disease entity during hospitalization can influence the risk of thrombosis, as can the duration of hospitalization [12].

As in a younger population, we found that minor injuries were associated with a higher risk of thrombosis over 3 months [8]. For minor injury, the time of highest risk differed than for other types of immobility, with a higher risk after 4 weeks compared with shortly after the minor injury. For the other studied factors, the risk was highest shortly after the exposure of immobility. It is possible that the seriousness of the minor injury, and the long-term consequences, influence the degree of immobility and increase the thrombotic risk, rather than the minor injury itself. It is also possible that this finding was a chance finding. Transient immobilization at home increased the risk of thrombosis 5-fold, and this risk was highest in the first 2 months after immobilization. Transient immobilization at home was most frequently due to infection, an important trigger for thrombosis [13].

The increased risk of thrombosis associated with out-of-hospital immobility indicates that prophylaxis may be beneficial. Home treatment with prophylaxis has effectively been implemented in other high-risk groups, such as orthopedic surgical patients [14]. The EXtended CLinical prophylaxis in Acutely Ill Medical patients (EXCLAIM) trial showed a beneficial effect of a longer duration of treatment within the older population (> 75 years) [15]. However, in two clinical trials including inpatients, extended thromboprophylaxis after discharge reduced thrombosis rates at the cost of higher bleeding rates (30-day event rate: 0.5%–0.8%) [16,17]. Other preventive measures that might be considered in this high-risk group include the use of graded elastic compression stockings or aspirin [18,19].

Recruiting older individuals in research is challenging [20]. We overcame this by performing home visits to assess the presence of risk factors. This enabled us to recruit less mobile individuals and achieve a high participation rate (participation rate: cases 68%, control subjects 73%). As in any case–control study, recall bias might have occurred. However, both cases and controls were interviewed by trained personnel using a standardized interview, which minimizes the risk of bias. Using an interview for assessment of risk factors for thrombosis within 3 months before the index date enabled us to determine putative risk factors, such as transient immobility at home, that might be challenging to determine (e.g. these are not mentioned regularly in medical reports and they might be difficult to recall precisely after a longer period). Unfortunately, data on preventive measures in the hospital (e.g. low molecular heparin injections) were not collected. However, individuals with in-hospital immobilization were most likely more often treated with thromboprophylaxis as their risk of venous thrombosis is thought to be increased. More frequent treatment with thromboprophylaxis in immobilized individuals, compared with individuals who are not immobilized, leads to an underestimation of the true relative risk of venous thrombosis associated with in-hospital immobilization.

In a case–control study, associations may be biased if the willingness to participate is affected by the presence of the risk factor. We minimized this bias by performing home visits and achieving a high participation.

Moreover, the sensitivity analysis in which we recalculated the index date of the control subjects did not alter interpretations of our results. We excluded cancer patients so our results are not generalizable to these individuals. Finally, a number of potential participants died before they could be invited to participate. The impact on our results is difficult to determine, but these participants were more likely to be immobilized, resulting in an underestimation of the true risk.

In conclusion, the contribution of immobility-related risk factors, defined as hospitalization, fracture, plaster cast (or splint), minor injury of the leg, and transient immobilization at home, to the risk of venous thrombosis in the older population is high. Studies regarding preventive measures during immobilization should focus on both in-hospital and out-of-hospital patients.

Addendum

M. J. Engbers and A. van Hylckama Vlieg had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: M. J. Engbers, A. van Hylckama Vlieg, J. W. Blom, M. Cushman, and F. R. Rosendaal. Acquisition of data: M. J. Engbers, A. van Hylckama Vlieg, M. Cushman. Analysis and interpretation of data: M. J. Engbers, A. van Hylckama Vlieg, J. W. Blom, M. Cushman, and F. R. Rosendaal. Drafting of the manuscript: M. J. Engbers, A. van Hylckama

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Vlieg, and J. W. Blom. Critical revision of the manuscript for important intellectual content: M. J. Engbers, A. van Hylckama Vlieg, J. W. Blom, M. Cushman, and F. R. Rosendaal. Statistical analysis: M. J. Engbers, A. van Hylckama Vlieg, and J. W. Blom. Obtained funding: A. van Hylckama Vlieg, F. R. Rosendaal, and M. Cushman. Administrative, technical, or material support: M. J. Engbers, A. van Hylckama Vlieg, J. W. Blom, M. Cushman, and F. R. Rosendaal. Study supervision: A. van Hylckama Vlieg, M. Cushman, and F. R. Rosendaal.

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Disclosure of Conflicts of Interest

The authors state that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Flowchart of AT-AGE study per center.

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